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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/029,016	12/20/2001	Anthony J. Celeste	5205BD1	4438

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/029,016	CELESTE ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,26,35,36,41,42,45-48 and 53-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,26,35,36,41,42,45-48 and 53-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0606*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 06/12/2006 has been entered. Claims 25–26, 35–36, 41–42, 45–48, and 53–60 are pending and being examined.

Terminal Disclaimer

The terminal disclaimer filed on 06/12/2006 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of 6,340,668 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Maintained Formal Matters, Objections, and/or Rejections:

Claims 25–26, 35–36, 41–42, 45–48, and 53–60 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method of promoting the survival of PC-12 cells under serum-free conditions by administering a BMP-11 comprising an amino acid sequence selected from the group consisting of amino acids 7 to 108 of SEQ ID NO: 11 or amino acids 1 to 109 of SEQ ID NO: 11, does not reasonably provide enablement for a method of promoting the survival of neuronal cells by administering a BMP-11 comprising an amino acid sequence encoded by a nucleotide sequence that hybridizes under the recited stringent conditions with the complement of nucleotides 778 to 1083 of SEQ ID NO: 10 or a nucleotide sequence that encodes the same amino acid sequence as nucleotides 778 to 1083 of SEQ ID NO: 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The examiner has maintained the rejection over the scope of the hybridization conditions, narrowed the scope of the previously indicated enabled functional activity, and relied on new

evidence to support the narrowing of the scope of the previously indicated enabled functional activity.

Applicants argue that although the bovine and human BMP-11 mature polypeptides are identical, applicants have provided nucleic acid sequences, which are 92.7% identical, encoding bovine and human BMP-11. Applicants argue that because these nucleic acid sequences are reduced to practice, the specification provides a repeatable, predictable process of producing variant BMP-11s. Applicants recognize that not all the hybridizing polynucleotides will necessarily encode a polypeptide that promotes cell survival. However, Applicants argue that predictability is not dispositive of enablement. Applicants argue that the examiner has failed to establish why it would be necessary to determine which amino acid residues are required for the functional and structural integrity of BMP-11 having the amino acid sequence of SEQ ID NO: 11. Applicants argue that such information is readily available to ordinarily skilled artisans given the specification's teachings and the level of skill and knowledge in the art. Applicants argue that although BMPs are heterogeneous with regard to their biological effects, they were well known to share common structural features essential for the function of each BMP. Applicants argue that the specification provides a repeatable process, predictable, and well-known process for generating polynucleotides that encode polypeptides that share common structural features because the hybridization and expression experiments require a low quantity of experimentation because they are likely to succeed. Applicants argue that the specification provides a great deal of guidance. Applicants argue that the hybridization conditions of the claims require 92% [nucleotide sequence] identity.

Applicants' arguments have been fully considered but they are not persuasive. The following passages from the specification seem most relevant for construing the term "BMP-11":

> Further included in the present invention are DNA sequences which hybridize under stringent conditions with the DNA sequence of SEQ ID NO: 1 or SEQ ID NO: 10 and encode a protein having BMP-11 activity. Finally, allelic or other variations of the sequences of SEQ ID NO: 1 or SEQ ID NO: 10, whether such nucleotide changes result in changes in the peptide sequence or not, but where the peptide sequence still has BMP-11 activity, are also included in the present invention. Page 9, lines 4-11.

> The BMP-11 proteins provided herein also include factors encoded by the sequences similar to those of SEQ ID NO: 1 or SEQ ID NO: 10, but into which modifications are naturally provided (e.g. allelic variations in the nucleotide sequence which may result in amino acid changes in the polypeptide) or deliberately engineered. For example, synthetic polypeptides may wholly or partially duplicate continuous sequences of the amino acid residues of SEQ ID NO: 2 or SEQ ID NO: 11. These sequences, by virtue of sharing primary, secondary, or tertiary structural and conformational characteristics with inhibin-.beta. polypeptides of SEQ ID NO: 2 or SEQ ID NO: 11 may possess BMP-11 activity in common therewith. Thus, they may be employed as biologically active substitutes for naturally-occurring BMP-11 polypeptides in therapeutic processes. Paragraph bridging pages 12-13.

> Similarly, DNA sequences which code for BMP-11 proteins coded for by the sequences of SEQ ID NO: 1 or SEQ ID NO: 10, but which differ in codon sequence due to the degeneracies of the genetic code or allelic variations (naturally-occurring base changes in the species population which may or may not result in an amino acid change) also encode the novel factors described herein. Variations in the DNA sequences of SEQ ID NO: 1 or SEQ ID NO: 10 which are caused by point mutations or by induced modifications (including insertion, deletion, and substitution) to enhance the activity, half-life or production of the polypeptides encoded are also encompassed in the invention. Page 14, full paragraph 1.

Accordingly, the claims are directed to or encompass a genus of variant BMP-11s encompassed by the hybridizing polynucleotides that encode a corresponding number of amino acid substitutions, insertions, deletions, and truncations with respect to the amino acid sequence of SEQ ID NO: 11. The claims also require that the variant BMP-11 promote the survival of any and/or all neuronal cells in culture.

Regarding the production of functional variant polypeptides, there is a lack of predictability in the art. Predicting structure, hence function, from primary amino acid sequence data is extremely complex and there doesn't exist an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. See Bowie (Science, (1990 Mar 16) 247 (4948) 1306-10) page 1306, column 1, full paragraph 1, or Ngo (The Protein Folding Problem and Tertiary Structure Prediction, Merz and Le Grand (Eds), August 1994, Springer Verlag, pages 433 and 492-495) page 433, full paragraph 1, and page 492, full paragraph 2.

The specification discloses only two species of BMP-11 that are identical, i.e., non-variant, in the mature, active region of the molecule. The specification lacks guidance for making, and working examples of, variant BMP-11s that promote the survival of any and/or all neuronal cells in culture. The examiner is aware that working examples are not required. Lack of a working example, however, is a factor to be considered. In the absence of such guidance, as skilled artisan is left to an extensive amount of random, trial and error experimentation wherein variant BMP-11s are randomly made and tested for the desired functional activity. Such extensive, random, trial and error experimentation is considered undue. It would be necessary to determine which amino acid residues in SEQ ID NO: 11 are required for the functional and structural integrity of a BMP-11 because such information would be required before a skilled artisan could even begin to rationally design a variant BMP-11 with any reasonable expectation that such a variant would have the desired functional activity. Although BMPs are known to share common structural features, the claims are not limited to a genus of BMP-11s that share common structural features essential for the function of each BMP-11 and, as discussed below, the effects of different BMPs on neuronal cells are unpredictable. Hence, it is not apparent what

shared common structural features essential for the function of each BMP in general, or BMP-11 in particular, contribute their effects on neuronal cells when the effects of different BMPs on neuronal cells are unpredictable. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Regarding the ability to promote the survival of any and/or all neuronal cells in culture, Jordan (European Journal of Neuroscience, (1997 Aug) 9 (8) 1699-709) teaches that:

> BMPs 9 and 11 did not promote the in vitro survival of dopaminergic neurons (page 1703, paragraph bridging left and right columns).
>
> BMP-11 had no effect on BrdU incorporation and astroglial cell maturation, indicating that not all members of the BMP family share effects on proliferation and differentiation of cells in the astrocyte lineage (page 1703, right column, full paragraph 1).
>
> BMPs are distinct from each other with regard to their neurotrophic potentials (page 1705, left column, full paragraph 1).
>
> The BMPs are heterogeneous with regard to their biological effects (paragraph bridging pages 1705-1706).

Farkas (Neuroscience. 1999;92(1):227-35) teaches that BMP-11 did not significantly promote the survival of chick DRG neurons *in vitro* (page 231, Figure 3E).

Wu (Neuron. 2003 Jan 23;37(2):197-207) provides evidence that in the olfactory epithelium (OE), generation of new neurons by neuronal progenitors is inhibited by growth and differentiation factor 11 (GDF11/BMP11) (Abstract).

Ge (Mol Cell Biol. 2005 Jul;25(14):5846-58) teaches that GDF11/BMP11 inhibits neurodifferentiation and that this inhibition is not limited to olfactory epithelium, as exogenously added active GDF11 inhibits nerve growth factor (NGF)-induced differentiation of PC12 cells to a neural-tissue-like phenotype (paragraph bridging pages 5846-5847).

Jordan, Farkas, Wu, and Ge are evidence that the effects of BMPs on neuronal cells are unpredictable and that a skilled artisan could not extrapolate the *in vitro* effects of BMP-11 on PC12 cells to its effects on any and/or all neuronal cells. The specification does not contain any working examples of the promotion of the survival of any other neuronal cell besides PC12 cells. The specification lacks guidance for promoting the survival of any and/or all neuronal cells with a factor that does not promote the survival of any and/or all neuronal cells.

Jordan, Farkas, Wu, and Ge are evidence that it is highly improbable that BMP-11 or any one of the variant BMP-11s will more likely than not perform in the manner disclosed and the present specification does not provide the guidance needed to predictably alter that sequence with any reasonable expectation that the resulting protein will promote the survival of any and/or all neuronal cells.

In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, and the unpredictability in the art, the skilled artisan is left to perform an undue amount of unduly extensive experimentation in order to practice the full scope of the claimed invention. It would require undue experimentation for the skilled artisan to use the full scope of the claimed invention.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

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CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

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5 DSR
AUGUST 16, 2006

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